Enabling future manufacture of dose forms: screening tools for an HME-3D printing process

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Introduction

Linking a hot-melt-extrusion (HME) process to 3D printing offers the ability for rapid prototyping of dose forms, whilst also allowing for personalisation of the dosage form to the patient's needs. However, process development can be lengthy and laborious since current technology involves process development for the HME and fused filament fabrication (FFF) process via the filament as an intermediate product.

This work aims to develop screening tools to understand and predict API-polymer behaviour in HME and FFF processes and therefore reducing development time and resource.

Methodology

Filaments for FFF with drug loadings ranging from 5 to 50 wt% of a model API-polymer system (HPMC, Affinisol 15LV) were produced by HME (Fig.1). Filaments were characterised by thermal, rheological and mechanical analysis.

Combining the melt rheology and mechanical data allowed us to identify mechanical and rheological limits for this API-polymer system that ensure the printability of these filaments

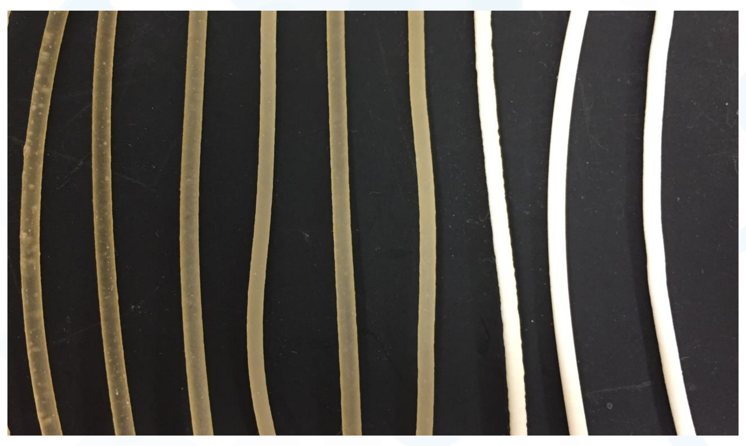
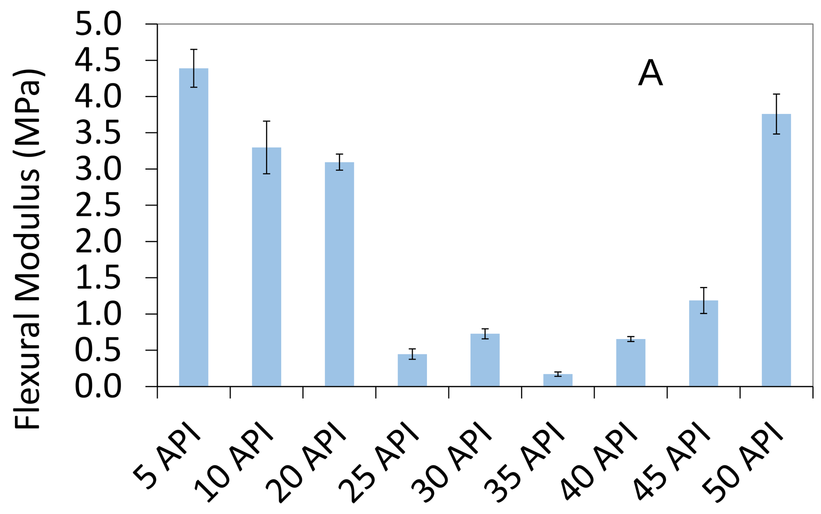


Figure 1: 5 - 50 wt% API-polymer filaments.

Thermal and Mechanical testing

Thermal properties of the extruded API-polymer system, showed three distinct groupings: sub-saturated, saturated and supersaturated systems. These mechanical data discerned between polymer dominated, plasticised polymer and crystalline dominated flexural behaviour (Fig.2) [1].



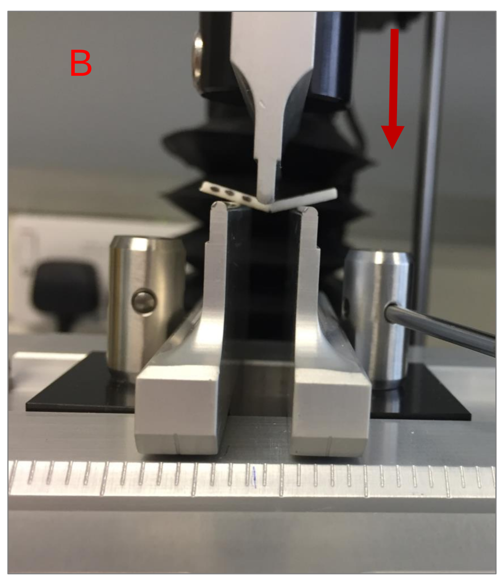
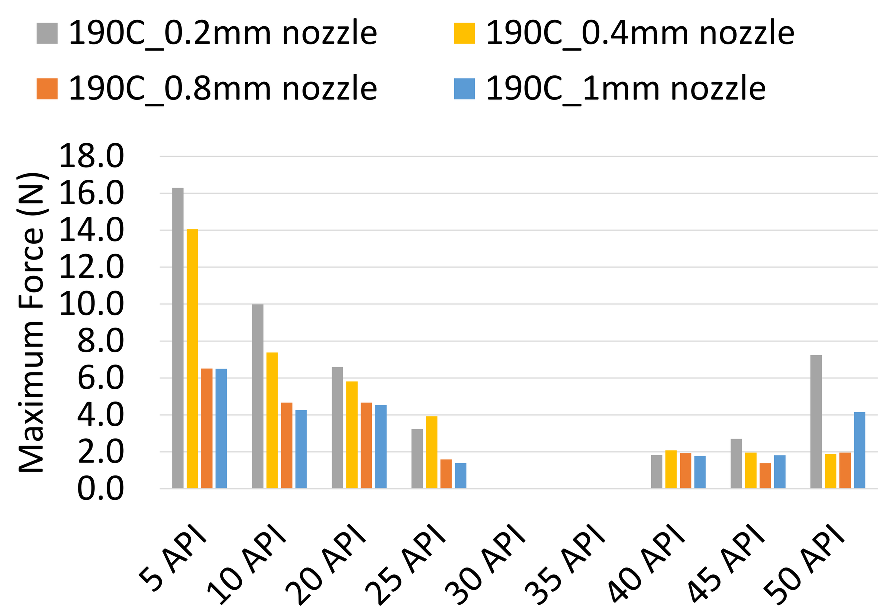


Figure 2: A) Flexural modulus of filaments. B) mini 3-point bend test setup.

Mechanical assessment of print process

Forces up to 16N were required for filaments with the highest polymer content. 30 and 35% drug loaded filaments failed to extrude due to the filament buckling between the pinch wheel and the liquefier entry (Fig.3, 6).



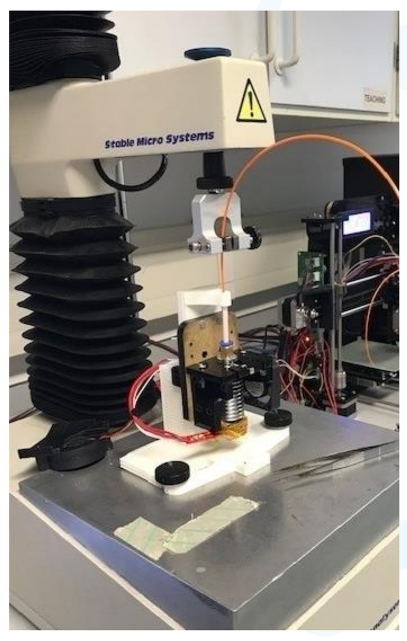


Figure 3: Printability – Maximum force required to extrude filaments through an FFF print head at 190°C.

Rheology Temperature sweep

A reduction in viscosity with increasing drug loading was observed as a vertical downwards shift of the temperature viscosity curves.

Onset of crystallisation in the polymer matrix was inhibited up to 40% drug loading across 190-95°C (Fig.4).

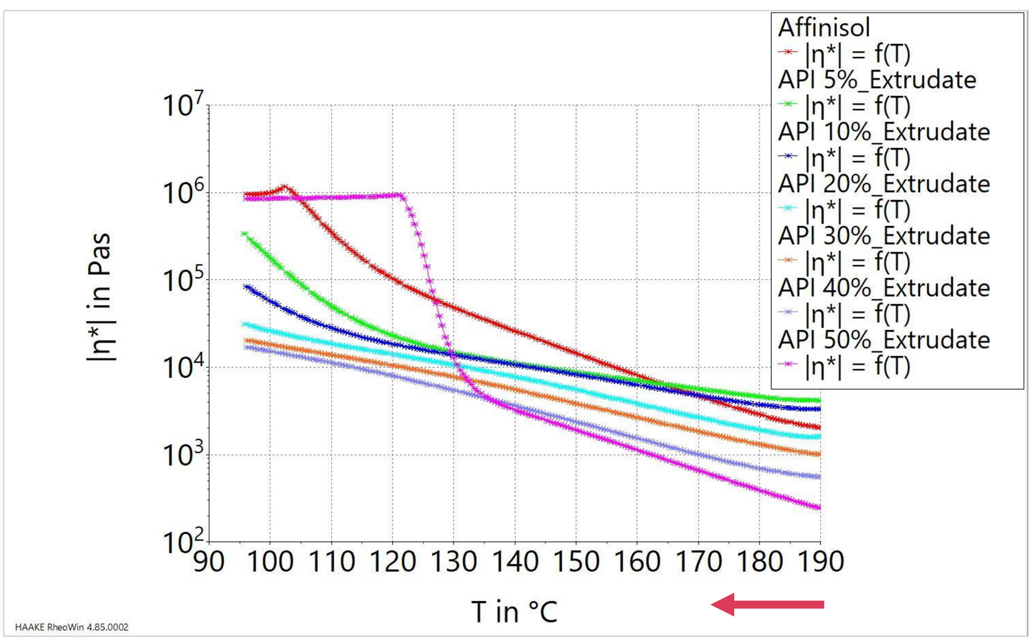


Figure 4: Oscillatory Temperature sweep, 190°C – 95°C, of polymer and API-polymer extrudates.

Rheology Frequency sweep

Shear thinning behaviour was observed. This was strongest for sub-saturated systems, seen as a steeper slope.

No change in slope was observed for drug loadings ≥20% (equilibrium solubility).

Supersaturated systems, drug loadings above 20%, showed a vertical downward shift in frequency viscosity curves (Fig.5).

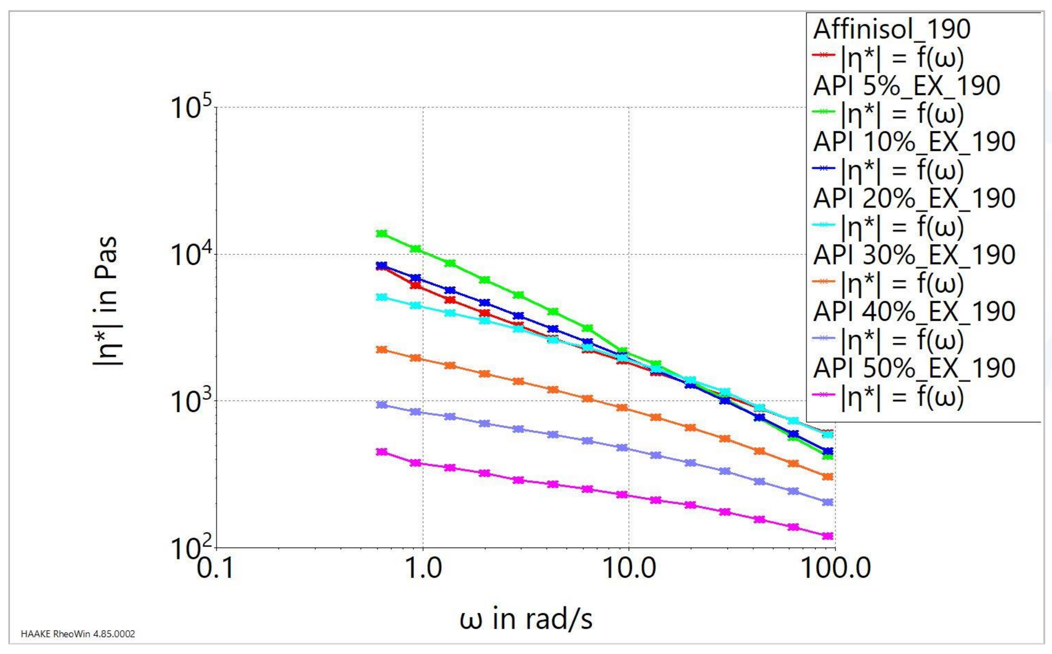


Figure 5: Oscillatory Frequency sweep of polymer and API-polymer extrudates at 190°C.

Results – Predicting printability

Printability prediction was based on two criteria: the force exerted on the filament between the pinch wheels and the entry of the liquefier not exceeding the buckling force in a print head (Fig.6) (buckling criterion for elastic columns) and the pressure drop within the liquefier required to drive the filament in the fused state (non-Newtonian fluid through a tube) (1) [2,3]:

$$\frac{E\gamma}{\eta} < \gamma Q l \left(\frac{L}{(Rr^2)}\right)^2 \qquad (1)$$

Eγ = Young's Modulus, η = apparent viscosity, γ = shear rate, Q = volumetric flowrate, L = Length distance between rollers and liquefier entry, R = radius of filament, r, l = radius and length of liquefier space;

If the ratio of Eγ/η is exceeded, extrusion may fail due to buckling.

The Cox-Merz-Rule was applied to the complex viscosity data and the buckling ratio, Eγ/η, plotted against the shear rate (Fig.7). The threshold buckling ratio was determined empirically (30% API).

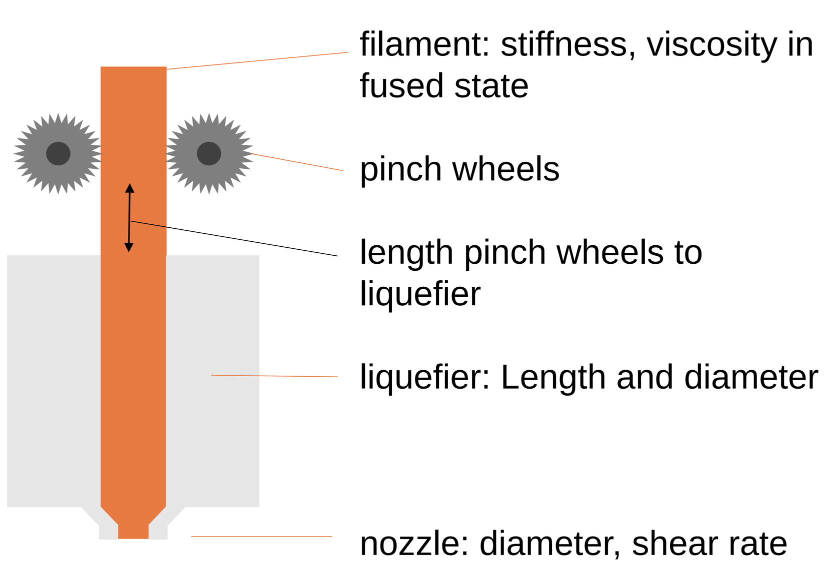


Figure 6: Schematic of an FFF liquefier showing important process and material parameters involved in buckling.

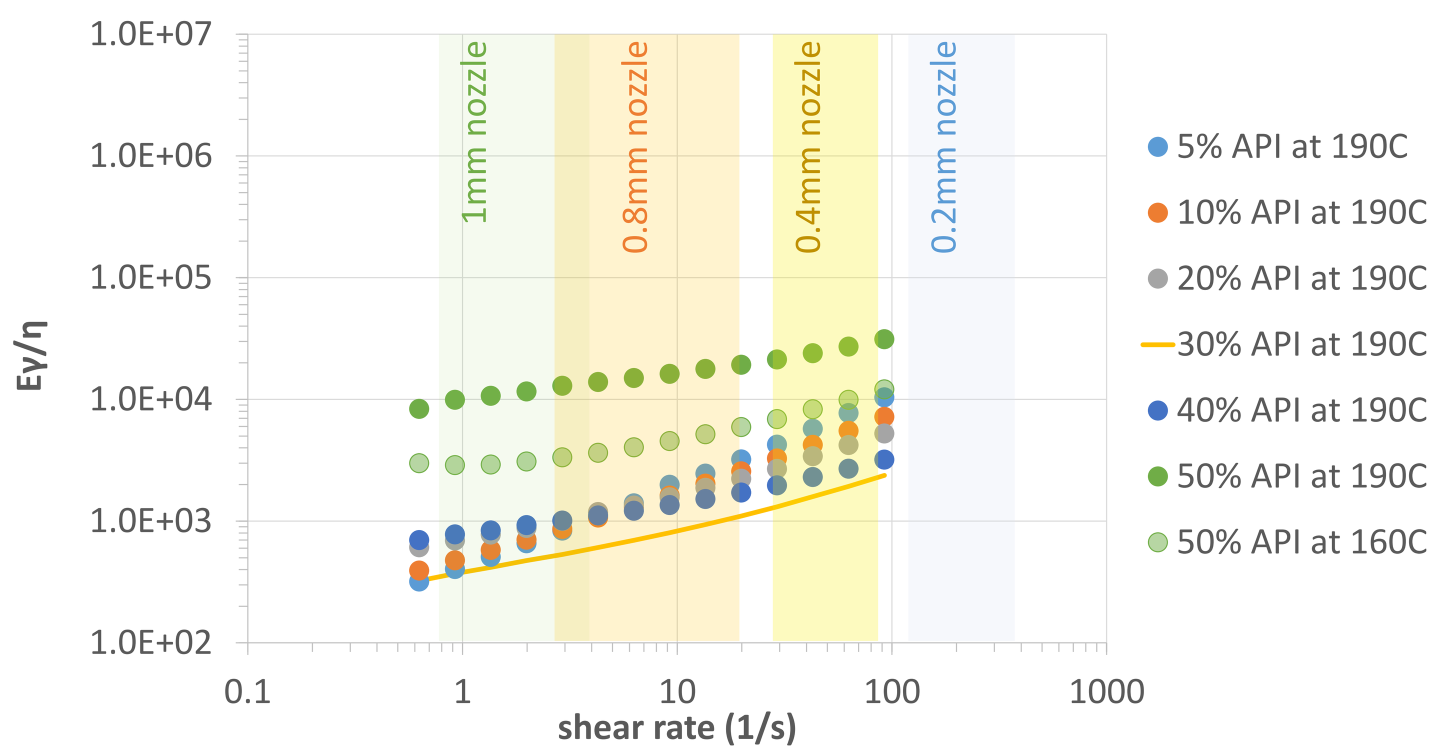


Figure 7: Printability prediction: ratio Eγ/η versus shear rate; Filament buckles with Eγ/η ≤ 30% API (yellow line); shear rates in print geometries with nozzle sizes of 1 mm are shaded green, 0.8mm - orange, 0.4 mm - yellow and 0.2 mm - blue with volumetric flow rates from 1.2 – 4.8 mm³/s.

Conclusions

Printability prediction based on the Eγ/η ratio is in good agreement with experimental printability data and could substantially reduce development time and material required for HME and FFF printing applications.

Future work

Further evaluation of API-polymer interaction and behaviour in HME and FFF applications are required to validate our findings.

References:

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3. Abouzaid, K., et al. (2018). "Printability of co-polyester using fused deposition modelling and related mechanical performance." *European Polymer Journal, 108, 262-273.*